# Complete Summary

## GUIDELINE TITLE

Bortezomib in multiple myeloma and lymphoma.

## BIBLIOGRAPHIC SOURCE(S)

Reece D, Kouroukis T, Haynes AE, Imrie K. Bortezomib in multiple myeloma and lymphoma. Toronto (ON): Cancer Care Ontario (CCO); 2008 Nov 24. 41 p. (CED-CCO special advice report; no. 11). [33 references]

## GUIDELINE STATUS

This is the current release of the guideline.

The CED-CCO Special Advice report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

## COMPLETE SUMMARY CONTENT



## SCOPE

### DISEASE/CONDITION(S)

- Multiple myeloma
- Lymphoma
- Waldenstrom's macroglobulinemia

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

### CLINICAL SPECIALTY

Oncology

### INTENDED USERS

Physicians

### GUIDELINE OBJECTIVE(S)

- To evaluate the efficacy of bortezomib alone or in combination in patients with multiple myeloma, Waldenstrom's macroglobulinemia, or lymphoma, as measured by survival, quality of life, disease control (e.g., time-to-progression), response duration, or response rate
- To evaluate the toxicity associated with the use of bortezomib
- To determine which patients are more or less likely to benefit from treatment with bortezomib

### TARGET POPULATION

Adult patients with multiple myeloma, Waldenstrom's macroglobulinemia, or lymphoma of any type, stage, histology, or performance status

### INTERVENTIONS AND PRACTICES CONSIDERED

1. Bortezomib plus pegylated liposomal doxorubicin (PLD)
2. Bortezomib monotherapy
3. Thalidomide, oral alkylating agent-based chemotherapy, or repeat transplantation
4. Bortezomib, melphalan, and prednisone

### MAJOR OUTCOMES CONSIDERED

- Survival
- Quality of life
- Disease control (e.g., time-to-progression)
- Response duration
- Response rate
- Toxicity

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

## DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (Ovid) (October 2004 through September Week 2 [September 22] 2008), MEDLINE Daily Update (September 22, 2008), MEDLINE In-Process & Other Non-Indexed Citations (September 22, 2008), EMBASE (Ovid) (2004 Week 42 through Week 38 [September 22]), and the Cochrane Library (2008, Issue 4) databases were searched. The search strategies for MEDLINE and EMBASE are shown in Appendix 1 in the original guideline document. Search strategies in other databases were similar.

In addition, conference proceedings of the American Society of Clinical Oncology (2005-2008) and the American Society of Hematology (2005-2007) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guideline Clearinghouse (http://www.guideline.gov/), and the National Institute for Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

### Study Selection Criteria

#### Multiple Myeloma

*Inclusion Criteria*

Articles were selected for inclusion in this systematic review of the evidence if they were published full report articles or published meeting abstracts of:

1. Systematic reviews, meta-analyses, or clinical practice guidelines of bortezomib in adult patients with multiple myeloma.
2. Randomized studies including adult patients with multiple myeloma and evaluating bortezomib as a single agent or in combination with other regimens.
3. Trials could compare bortezomib to any agent, any combination of agents, or placebo.
4. Results reporting one or more of the following outcomes: survival, quality of life, disease control (e.g., time-to-progression [TTP]), response duration, response rate, or adverse effects.

*Exclusion Criteria*

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English, due to financial considerations.

#### Lymphoma

*Inclusion Criteria*

Articles were selected for inclusion in this systematic review of the evidence if they were published full report articles or published meeting abstracts of:

1. Systematic reviews, meta-analyses, or clinical practice guidelines of bortezomib in adult patients with Waldenstrom's macroglobulinemia or lymphoma.
2. Studies including adult patients with Waldenstrom's macroglobulinemia, or lymphoma (any histologic subtype, stage, performance status, or disease type).
3. Randomized trials in which bortezomib could be compared with any agent, any combination of agents, or placebo.
4. Single-arm phase II trials evaluating bortezomib as a single agent or in combination with other regimens.
5. Results reporting one or more of the following outcomes: survival, quality of life, disease control (e.g., time-to-progression [TTP]), response duration, response rate, or adverse effects.

*Exclusion Criteria*

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Single-arm phase II trials reporting fewer than 20 patients (all disease types combined).
3. Abstract reports of single-arm phase II trials that have not been previously fully published.
4. Phase I trials.

## NUMBER OF SOURCE DOCUMENTS

### Multiple Myeloma

A total of 327 citations of studies that included patients with multiple myeloma were identified from the Medline, EMBASE, and Cochrane library databases. From those citations, a total of seven full publications met eligibility criteria and were included. In addition 117 abstracts presented at American Society of Hematology (ASH) or American Society of Clinical Oncology (ASCO) were identified. Seventeen abstracts met the eligibility criteria and were included. In total, five unique trials were identified from the seven full publications and 17 abstracts.

### Lymphoma and Waldenstrom's Macroglobulinemia

A total of 368 citations of studies that included patients with lymphoma or Waldenstrom's macroglobulinemia (WM) were identified from the Medline, EMBASE, and Cochrane library databases. From those citations, a total of seven full publications met eligibility criteria and were included. In addition, 155 abstracts presented at American Society of Hematology or American Society of Clinical Oncology were identified. Three abstracts of two randomized trials and one abstract providing updated data for a previously fully published single-arm

phase II trial met the eligibility criteria and were included. In total, two phase II randomized trials and seven fully published single arm phase II trials were identified.

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

## METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data appropriate for pooling or meta-analysis are not expected but will be investigated if the possibility exists. For planned analyses, the primary outcome of interest is progression-free survival, secondary outcomes of interest are response rate and overall survival, and subset analyses will be conducted by histology.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

#### Multiple Myeloma – Relapsed and Refractory

- The combination of bortezomib and pegylated liposomal doxorubicin (PLD) is the recommended treatment option for patients with relapsed or refractory multiple myeloma refractory to or relapsing within one year of the conclusion of initial or after subsequent treatment(s) (including autologous stem cell transplantation) who are candidates for further chemotherapy who have received less than 240 mg/$m^2$, or the equivalent cumulative dose of doxorubicin, who have a left ventricular ejection fraction in the normal range, and who would be expected to tolerate the myelosuppression of combination therapy.
- For patients with myeloma refractory to or relapsing within one year of the conclusion of initial or after subsequent treatment(s) (including autologous stem cell transplantation) who are candidates for further chemotherapy and are not candidates for the combination of bortezomib and PLD, bortezomib monotherapy is recommended as the preferred treatment option.
- It is the opinion of the authors that bortezomib with or without PLD, as described above, is also a reasonable option for patients relapsing at least one year after initial therapy with or without autologous stem cell transplantation and that thalidomide, alkylating agents, or repeat transplantation may also be options for these patients. However, evaluation of these other options is beyond the scope of this report.

#### Multiple Myeloma - Previously Untreated

- For patients with previously untreated multiple myeloma who are ineligible for autologous stem cell transplantation, the combination of bortezomib, melphalan, and prednisone is an acceptable first-line treatment option and preferred over treatment with melphalan and prednisone alone.
- There is insufficient evidence at this time for any recommendations regarding the use of bortezomib prior to autologous stem cell transplantation in patients with previously untreated multiple myeloma.

#### Lymphoma and Waldenstrom's Macroglobulinemia

- For patients with relapsed or refractory mantle cell lymphoma, bortezomib monotherapy is a reasonable treatment option.
- There is insufficient evidence to support the use of bortezomib outside of clinical trials in patients with previously untreated mantle cell lymphoma or other lymphoma histologies.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized and non-randomized trials.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate use of bortezomib in patients with multiple myeloma, including improved quality of life, and prolonged survival

### POTENTIAL HARMS

See the original guideline document for a detailed review of the toxicities observed in the trials reviewed.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- Consideration should be given to the use of antiviral prophylaxis against shingles as it is now recognized to occur more frequently during bortezomib therapy in patients with multiple myeloma.
- Another systematic review has provided a summary of the evidence for the use of melphalan, prednisone and thalidomide (MPT) as preferred initial therapy for patients with myeloma who are not candidates for an autologous stem cell transplant. There is no direct comparison of thalidomide versus bortezomib in combination with melphalan and prednisone for initial therapy in such patients. As the volume of data is greater with MPT, the authors would suggest a preference for MPT as initial therapy for such patients. However, thalidomide may not be easily available and practitioners may opt to treat certain patient subgroups with bortezomib containing initial therapy (e.g., those with adverse cytogenetic features).
- For specific details related to the administration of bortezomib therapy, the authors suggest clinicians refer to the protocols used in the major trials. Some of those details are provided below for informational purposes:
    - Regarding dosage, bortezomib 1.3 $mg/m^2$ is given as a rapid intravenous bolus over 3-5 seconds on days 1, 4, 8 and 11 of a 21-day cycle; a minimum of 72 hours between doses is required to allow for the recovery of normal proteasome function. Vital signs should be checked before and after each dose. A complete blood count is recommended before each dose, with blood chemistries, including electrolytes and creatinine levels, monitored at minimum on days 1 and 8 of each cycle. The dose of bortezomib should be reduced or held immediately for the development of painful neuropathy, as described in the product monograph; dose modification may also be required for

peripheral sensory neuropathy without pain, or other toxicities. Most toxicities are reversible if dose modification guidelines are followed.

**Multiple Myeloma**

- For the combination of bortezomib and pegylated liposomal doxorubicin (PLD) in relapsed/refractory myeloma, PLD 30 $mg/m^2$ is administered as a 1 hour infusion on day 4 of each 21-day cycle of bortezomib at the doses described above. Treatment should be continued for 8 cycles unless disease progression or unacceptable treatment-related toxicity occurs. In keeping with the design of the randomized controlled trial (RCT), patients who are still responding and who are tolerating therapy well may continue until the criteria of progressive myeloma are met, i.e., at least a 25% increase in the serum monoclonal protein level (which must be an absolute minimum increase of 5 g/L). Although not specified in the trial, it is the authors' opinion that treatment can be discontinued 2-4 cycles after achievement of complete remission (CR) (determined by negative electrophoresis and immunofixation).
- For the combination of bortezomib with melphalan and prednisone as initial therapy in patients who are ineligible for autologous stem cell transplantation, melphalan 9 $mg/m^2$ and prednisone 60 $mg/m^2$ are given on days 1-4 of a 6-week cycle. Bortezomib 1.3 $mg/m^2$ is administered intravenously on days 1, 4, 8, 11, 22, 25, 29 and 32 during cycles 1-4, and on days 1, 8, 22 and 29 of cycles 5-9. A total of 9 cycles is given.

**Lymphoma**

- For relapsed or refractory mantle cell lymphoma, treatment should continue until disease progression, intolerance, or until 2-4 cycles after maximal response has been achieved.

- Responses to treatment are usually apparent by six weeks (two cycles). For patients achieving complete remission, bortezomib should be given for two additional cycles beyond the date of confirmed complete remission. In patients with progressive disease after two cycles, or stable disease after four cycles, dexamethasone (20 mg orally the day of, and the day after each bortezomib dose) added to the bortezomib regimen may produce an objective response. Bortezomib (with or without dexamethasone) should be continued in patients showing benefit from therapy (excluding those in complete remission), unless disease progression or significant toxicity is observed. Therapy should be discontinued in patients who do not respond to bortezomib alone if disease progression is seen within two cycles of the addition dexamethasone.

- The authors recognize that thalidomide and lenalidomide are active agents in treating patients with multiple myeloma who have relapsed after autologous stem cell transplantation or are refractory to alkylating agent-based chemotherapy. To date, there are no randomized controlled trials comparing thalidomide or lenalidomide to bortezomib in this setting. Therefore, the

authors cannot make any conclusions regarding the use of one over the other.

### Disclaimer

Care has been taken in the preparation of the information contained in the report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better
Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

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### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2006 Apr 3 (revised 2008 Nov 24)

### GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

## GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

## SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

## GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The authors of this special advice report disclosed potential conflicts of interest relating to the topic of this evidence-based series. One author (DR) was the principal investigator or the local investigator and received research funding for four trials, including one of the randomized controlled trials (RCTs) in multiple myeloma (MM) reported here. That author was also a consultant for the manufacturer of bortezomib, was an advisory board participant for a future trial, and received honoraria. One other author (TK) received honoraria while acting as a consultant for the manufacturer of bortezomib and was an advisory board participant.

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## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

## AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on June 29, 2006. The updated information was verified by the guideline developer on July 7, 2006. This NGC summary was updated by ECRI Institute on September 24, 2009.

## COPYRIGHT STATEMENT



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